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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

KERR, KATHLEEN M

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 10/21/2003

15

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/775,938

Applicant(s)

HAYGOOD ET AL.

Examiner

Kathleen M Kerr

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 07 August 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 66,67,70-74 and 88 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 66,67,70-74 and 88 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☒ Other: **BLAST**.

DETAILED ACTION

Application Status

1. In response to the previous Office action, a non-final rejection (Paper No. 12, mailed on March 5, 2003), Applicants filed an amendment and response received on August 7, 2003 (Paper No. 14). Said amendment cancelled Claims 68-69, 75-87 and 89 and amended Claims 66, 67, 70-74, and 88. Thus, Claims 66, 67, 70-74, and 88 are pending in the instant Office action and will be examined herein.

Priority

2. As previously noted, the instant application is granted the benefit of priority of a continuation of the international application PCT/US00/21326 filed on August 4, 2000. The instant application is also granted the benefit of priority for the U.S. Provisional Application No. 60/147,283 filed on August 4, 1999; the Examiner notes that the elected SEQ ID NO:37 is NOT disclosed in this priority document.

Compliance with the Sequence Rules

3. By virtue of Applicants' amendment to the Brief Description of the Drawings, the instant application now fully complies with the sequence rules.

Withdrawn - Objections to the Specification

4. Previous objection to the specification because the title is not descriptive is withdrawn by virtue of Applicants' amendment.

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5. Previous objection to the Abstract for not completely describing the disclosed subject matter is withdrawn by virtue of Applicant's amendment.

6. Previous objection to the specification for being confusing and/or incomplete is withdrawn by virtue of Applicant's amendment.

Withdrawn - Claim Objections

7. Previous objection to Claims 66-74 and 86-88 for containing non-elected subject matter is withdrawn by virtue of Applicants' amendment.

8. Previous objection to Claims 69-74 under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn by virtue of Applicants' amendment or cancellation of said claims.

Withdrawn - Claim Rejections - 35 U.S.C. § 112, second paragraph

9. Previous rejection of Claims 66-74 and 86-87 under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "derived from" is withdrawn by virtue of Applicants' amendment. Moreover, amendments to Claims 70-74 clearly require that the nucleic acid molecule claimed be native to particular genera or organisms.

10. Previous rejection of Claims 66-74 and 86-87 under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "marine organism" is withdrawn by virtue of Applicants' amendment.

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11. Previous rejection of Claims 86-87 under 35 U.S.C. § 112, second paragraph, as being indefinite for the terms “moderate hybridization” and “stringent hybridization” is withdrawn by virtue of Applicants’ cancellation of said claims.

12. Previous rejection of Claims 86-87 under 35 U.S.C. § 112, second paragraph, as being indefinite for the use of the complement language is withdrawn by virtue of Applicants’ cancellation of said claims.

New or Maintained - Claim Rejections - 35 U.S.C. § 112, second paragraph

13. Previous rejection of Claims 66, 67, and 70-74 under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase “at least one polypeptide that catalyzes at least one step in the synthesis of at least bryopyran ring” is maintained. Applicants’ arguments have been fully considered but are not deemed persuasive for the following reasons.

Firstly, the Examiner notes that the amended language of “the at least one polypeptide comprises at least one activity of a polyketide synthase” adds to the confusion of the claim because a polypeptide does not “comprise” an activity; a polypeptide has an activity.

Applicants argue that the metes and bounds of the phrase is clear by virtue of the disclosure in Figure 2 showing domain structure of a polyketide synthase, including the activities of the domains. This is not the case. It is unclear if the activity in the claim is limited to those noted in Figure 2; limitations from the specification cannot be read into the claims. Moreover, polyketide synthases include not only the genes depicted in Figure 2 for a type I polyketide synthase, but also include other activities of other types of synthases encompassed by the term (type II and fungal polyketide synthases are known in the art to have different functional

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domains – see pages 15-16 of the instant specification). If Applicants mean to limit the activities of the polypeptide in the claim, the Examiner suggests inserting a clause that requires the activities in Figure 2. Additionally, the polypeptide must catalyze a step in the biosynthesis of a bryopyran ring; however, no such steps are defined.

Additionally, Applicants argue that Figure 2 describes the bryopyran polyketide synthase, this is not the case. Figure 2 depicts the erythromycin PKS. No analysis of SEQ ID NO:37 as it relates to the domain structure depicted in Figure 2 is described in the specification. Again, the Examiner notes that “*no encoded polypeptides* are defined from SEQ ID NO:37 and, more particularly, no polyketide synthase polypeptides are described as being encoded by SEQ ID NO:37. SEQ ID NO:37 is only defined as the sequence of 5B Pst A7 contig (see page 60). Thus, all claims relying on encoding a particular function are unclear in view of the instant specification.”

14. (New) Claims 66, 67, and 70-74 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The first occurrence of “or the complement thereof” is confusing since it is unclear which molecule is complemented. The Examiner suggests the following: ---comprising at least one isolated nucleic acid molecule, or the complement thereof, wherein said nucleic acid molecule encodes ...---.

15. (New) Claims 66, 67, and 70-74 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

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applicant regards as the invention. The hybridization conditions in Claim 66 are unclear because they are wash conditions as defined in the specification on page 9. Clarification is required.

Withdrawn - Claim Rejections - 35 U.S.C. § 112, first paragraph

16. Previous rejection of Claims 86-87 under 35 U.S.C. § 112, first paragraph, written description, is withdrawn by virtue of Applicants' cancellation of said claims.

New or Maintained - Claim Rejections - 35 U.S.C. § 112, first paragraph

17. Previous rejection of Claims 66, 67, and 70-74 under 35 U.S.C. § 112, first paragraph, written description, for having an *unclear function* and being *without any clear structural limitations* is maintained. Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicants argue that the amendment to the function and structure in Claim 66 limit the claim to nucleic acid molecules having a clear structure and function. This is not the case as noted above. Moreover, the function in the claims, if it were clear, is not specific since polyketide synthase domains have numerous activities, a few of which are noted in Figure 2. Thus, the structure, even if it were clearly defined by specific hybridization conditions or % identity limitations, is not bounded by a specific function that relates specifically to the structure.

As previously noted,

“the elected subject matter of SEQ ID NO:37 is described as the sequence of contig 5B Pst A7 that is involved in encoding polyketide synthase and/or bryopyran ring-containing compounds. No open reading frames are noted; thus SEQ ID NO:37 is not described as encoding a particular polypeptide. Moreover, this sequence is only described according to the putative and broad functional characteristics of the undescribed polypeptides SEQ ID NO:37 is purported to encode; no structural relationship is described or used in the claims.”

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18. (New) Claims 66, 67, and 70-74 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while possibly being enabling for nucleic acid molecules with a high degree of sequence identity to SEQ ID NO:37 and having the same function, does not reasonably provide enablement for nucleic acid molecules with the low degree of sequence identity claimed and having a vague function. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The amount of experimentation required of one of skill in the art to use the claimed invention to the full extent of its scope is undue. The instant rejection is set forth as if the utility rejection, maintained below, can be overcome in response to the instant Office action.

The factors to be considered in determining whether undue experimentation is required are summarized in *re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988). The court in *Wands* states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the

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relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a prima facie case are discussed below.

Applicants present no guidance or working examples of the use of polynucleotides that have such low sequence identity with respect to SEQ ID NO:37. The nature of the invention is such that the DNA is purported to encode type I polyketide synthase proteins, and with such a great deviation from the known sequence, the predictability of functionality becomes extremely low. Such enormous breadth and unpredictability renders the instant claims not enabled to the full extent of their scope without undue experimentation. While the instant specification may describe and enable means for identifying other PKS genes using hybridization methods, etc., these methods do not enable one of skill in the art to make all, or a relevant portion of, the polynucleotides within the scope of the claims because the ability to find a PKS gene, which is structurally related to SEQ ID NO:37, is not equivalent to the ability to make a PKS gene as required by the statute (i.e., "make and use"). No description in the specification provides particular residues whose encoding is important within the disclosed sequence so that its PKS-nature is maintained. Thus, one of skill in the art would be unable to predict the structure of the other members of the genus in order to make such members. Therefore, the instant claims are not enabled to the full extent of their scope.

Maintained - Claim Rejections - 35 U.S.C. § 101

19. Previous rejection of Claims 66, 67, 70-74 and 88 under 35 U.S.C. § 101 because the claimed invention is not supported by either a specific, asserted utility or a well established

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utility is maintained. Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicants argue that because the disclosed nucleic acid molecules encode polypeptides with homology to known proteins with known and well-established utilities, the claimed nucleic acid molecules also have utility per the Utility Guidelines (Federal Register, 2001). The Examiner agrees that if SEQ ID NO:37 could be established as encoding PKSs, by homology, the claimed nucleic acid molecules would have utility; however, Applicant's attention is drawn to the Guidelines that require the Office to "take into account both the nature and degree of the homology". No homology of SEQ ID NO:37 with PKS genes has been established. Figure 12 vaguely depicts a homology of contig 5B (SEQ ID NO:37) with PKSs, and Figure 13 vaguely depicts PKS homology with 5 regions of contig 5B; in neither case is the homology described. The specification implies the homologies are identified via BLAST. The Examiner performed such a homology search and found no homologies to known PKS genes (see attachment). Moreover, in the sequence searching of SEQ ID NO:37, no homologies to known type I PKSs were found.

In the Examples in the specification, some contigs are found using degenerate primers related to KS domains of type I PKSs (see pages 50-53); none of these contigs are SEQ ID NO:37. On page 59, mention of clone 5B and its homology to PKSs at its T7 end is described, but, again, no depiction of the homology or description of its extent is described. Again, the Examiner notes that a homology search by the Office did not identify PKS homology. Thus, the assignment of SEQ ID NO:37 as a PKS gene and/or gene cluster is not credible.

As previously noted, “[n]o open reading frames and/or encoded proteins are defined for SEQ ID NO:37. No specific function, such as encoding a ketosynthase-functioning enzyme, is proposed for SEQ ID NO:37. No tested functionality of SEQ ID NO:37 is offered, for example, transformation into a bryopyran-minus strain and screening for the introduction of the ability to produce bryopyran compounds.”

To overcome this rejection, the Examiner suggests that Applicants supply, by way of alignments and/or quoted percentages of homologies, the “PKS homology” noted in the specification for SEQ ID NO:37.

20. Previous rejection of Claims 66, 67, 70-74 and 88 under 35 U.S.C. 112, first paragraph, enablement, is maintained for the reasons noted above in the maintenance of the utility rejection. Moreover, the Examiner will comment further on the ability to use the claimed invention.

If SEQ ID NO:37 is homologous to known PKS genes, then Claim 88 would be allowable. One of skill in the art would be able to use portions of SEQ ID NO:37, for example a portion homologous to an AT domain of the erythromycin PKS gene cluster, in swapping experiments with other PKS gene clusters to produce polyketide analogs.

Withdrawn - Claim Rejections - 35 U.S.C. § 102

21. Previous rejection of Claims 66-69 and 86-87 under 35 U.S.C. § 102(b) as being anticipated by GenBank Accession Number U65015 as evidenced by Kerr *et al.* is withdrawn by virtue of Applicants’ amendment in Claim 66 with hybridization conditions outside the scope of the DNA of GenBank Accession Number U65015.

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Summary of Pending Issues

22. The following is a summary of the issues pending in the instant application:
- a) Claims 66, 67, and 70-74 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase “at least one polypeptide that catalyzes at least one step in the synthesis of at least bryopyran ring”.
 - b) Claims 66, 67, and 70-74 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the first occurrence of “or the complement thereof”
 - c) Claims 66, 67, and 70-74 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the hybridization conditions in Claim 66.
 - d) Claims 66, 67, and 70-74 stand rejected under 35 U.S.C. § 112, first paragraph, written description.
 - e) Claims 66, 67, and 70-74 stand rejected under 35 U.S.C. § 112, first paragraph, scope of enablement.
 - f) Claims 66, 67, 70-74 and 88 stand rejected under 35 U.S.C. § 101.
 - g) Claims 66, 67, 70-74 and 88 stand rejected under 35 U.S.C. 112, first paragraph, enablement.

Conclusion

23. Claims 66, 67, 70-74 and 88 are rejected for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R.

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§ 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



PONNATHAPUACHUTAMURTHY
SUPERVISORY PATENT EXAMINER
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KMK
October 15, 2003